m-/p-Cresol

CAS #1319-77-3
Swiss CD-1 mice, at 0.0, .25, 1.0, and 1.5% in feed
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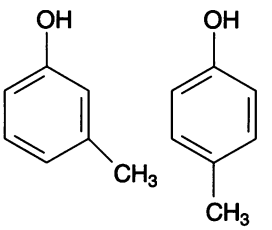

m- and p-cresol (MPC) are widely used in many applications including disinfectants, solvents, cleaners, motor oil additives, and even flavorings, and are also found in air and water. Preliminary data from a 90-day subchronic study suggested ovarian and uterine effects in Swiss CD-1 mice, along with lengthened estrous cycles. Thus, a mixture of these (MPC) two isomers was tested for its effects on reproduction and fertility in Swiss CD-1 mice using the RACB protocol. Data from a 2-week dose-range-finding study (Task 1) were used to set exposure concentrations for the Task 2 continuous cohabitation study at 0.25, 1.0, and 1.5% in feed. Based on mean feed consumption and body weight, the estimated doses were approximately 370, 1500, and 2100 mg/kg/day.

In the F_0 generation (Task 2) animals, three, one, one, and two females died during Task 2 in the control through high dose groups. The causes of death could not be determined, except for an additional control male where the cause of death was trauma. The lack of a dose relationship suggests that these deaths were not MPC-related.

During Task 2, there was no effect on the number of litters per pair, while the number of live pups per litter was reduced by approximately 20% at the high dose, and pup weight adjusted for litter size was reduced at this dose by 5%. Also at the high dose, the cumulative days to deliver each litter was increased by 1 to 4 days. Postpartum dam weight was reduced at the high dose by approximately 10%, after all litters, while male weight was similarly reduced at these intervals also.

The last litter was reared by the dam until weaning at postnatal day 21. Lactating dam weights were reduced by approximately 3% and approximately 12% in the middle and high dose groups, respectively. While pup viability was unaffected by MPC exposure, pup body weights were significantly lower than controls after postnatal day 7 in the middle and high dose groups. By postnatal day 21, body weights in the low to high dose group pups were reduced by approximately 10, 28, and 23%.

Because of the reduction in pup number seen in Task 2, a crossover Task 3 was performed using the control and high dose animals. Surprisingly, there were no changes in any fertility or reproductive end point except that body weight for the pups from either treated males or treated females was reduced by 6 to 8%. Pup number and viability were unaffected.

After the Task 3 litters were delivered and evaluated, the F_0 adults were killed and necropsied. Male body weight was reduced by approximately 10% at the top dose, while adjusted kidney weight and liver weight were increased by approximately 6 and 26%, respectively. Seminal vesicle weight was reduced at the high dose by approximately 10%. There were no changes in sperm end points (count, motility, morphology, testicular spermatid head counts).

Female body weight at the high dose was reduced by approximately 10%, while adjusted liver weight was increased by approximately 20%. No changes in estrous cycles were detected.

No treatment-related histologic changes were detected microscopically in high-dose animals, compared to controls.

Fertility was evaluated at all dose levels in the second generation. The only adverse effect noted was a 13% reduction in adjusted pup weight at the high dose. Feed and water consumption were variably increased in all dose groups at different times; estimated consumption of MPC was approximately 450, 1700, and 2400 mg/kg/day.

After the F_2 pups were delivered and evaluated, the F_1 adults were killed and necropsied. Male body weights were reduced by approximately 10 and 14% in the middle and high dose groups, respectively, while absolute testis weight was reduced in those groups by 10 and 8%. In the middle and high dose groups, adjusted liver weight was increased by 15 and 18%, and seminal vesicle weights were reduced by 12 and 10%, respectively. Only at the high dose, male kidney weight was increased by approximately 14%, while prostate weight was reduced by 18%. There were no MPC-related differences in sperm end points. In females, body weight was reduced by 6 and 13% in the middle and high dose groups, respectively. As dose increased, relative liver weight was increased by 11, 20, and 23%, while kidney weight increased by 9, 7, and 9%. Estrous cycle lengths were unchanged at any dose of MPC tested in this study. while there was a dose-related increase in hydronephrosis that appeared significant at the high dose (4/40 control vs 10/20 high dose MPC), no other significant microscopic lesions were found.

Thus, this study found that a mixture of m- and p-cresols was a reproductive toxicant in Swiss CD-1 mice, as evidenced by fewer F_1 pups per litter, and reduced pup weight in both generations. There were also reductions in the weights of reproductive organs at necropsy at the high (F_0) or middle and high (F_1) dose levels. However, changes in pup growth and weights of somatic organs occurred at all dose levels. Thus, meta- and para-cresol is not selective reproductive toxicant in Swiss CD-1 mice.

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **PB92191741**
Chemical: **m-/p-cresol**
CAS#: **1319-77-3**
Mode of exposure: **Feed**
Species/strain: **Swiss CD-1 mice**

F_0 generation — Dose concentration →	0.25%	1.0%	1.5%
General toxicity	Male, female	Male, female	Male, female
Body weight	—, —	—, —	↓, ↓
Kidney weight[a]	—, —	—, —	↑, —
Liver weight[a]	—, —	—, —	↑, ↑
Mortality	—, —	—, —	—, —
Feed consumption	—, —	—, —	—, —
Water consumption	—, —	—, —	—, —
Clinical signs	—, —	—, —	—, —
Reproductive toxicity			
x̄ litters/pair	—	—	—
# live pups/litter; pup wt./litter	—, —	—, —	↓, ↓
Cumulative days to litter	—	—	↑
Absolute testis, epididymis weight[a]	—, —	—, —	—, —
Sex accessory gland weight[a] (prostate, seminal vesicle)	—, —	—, —	—, ↓
Epidid. sperm parameters (#, motility, morphology)	—, —, —	—, —, —	—, —, —
Estrous cycle length	•	•	—

Determination of affected sex (crossover)	Male	Female	Both
Dose level	—	—	1.5%

F_1 generation — Dose concentration →	0.25%	1.0%	1.5%
General toxicity	Male, female	Male, female	Male, female
Pup growth to weaning	↓, ↓	↓, ↓	↓, ↓
Mortality	—, —	—, —	—, —
Adult body weight	—, —	↓, ↓	↓, ↓
Kidney weight[a]	—, ↑	—, ↑	↑, ↑
Liver weight[a]	—, ↑	↑, ↑	↑, ↑
Feed consumption	—, ↑	↑, —	↑, —
Water consumption	↑, —	—, —	↑, —
Clinical signs	—, —	—, —	↑, ↑
Reproductive toxicity			
Fertility index	—	—	—
# live pups/litter; pup wt./litter	—, —	—, —	—, ↓
Absolute testis, epididymis weight[a]	—, —	↓, —	↓, —
Sex accessory gland weight[a] (prostate, seminal vesicle)	—, —	—, ↓	↓, ↓
Epidid. sperm parameters (#, motility, morphology)	—, —, —	—, —, —	—, —, —
Estrous cycle length	—	—	—

Summary information	
Affected sex?	**Both**
Study confounders:	**None**
NOAEL reproductive toxicity:	**0.25%**
NOAEL general toxicity:	**<0.25%**
F_1 more sensitive than F_0?	**Yes**
Postnatal toxicity:	**Yes**

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); —, —, no change in males or females. [a]Adjusted for body weight.